

Stability of extemporaneously prepared rosuvastatin oral suspension

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Purpose. The stability of an extemporaneously prepared rosuvastatin suspension stored over 30 days under various storage conditions was evaluated.

Methods. Rosuvastatin suspension was extemporaneously prepared using commercial rosuvastatin tablets as the source of active pharmaceutical ingredient. The organoleptic properties, dissolution profile, and stability of the formulation were investigated. For the stability studies, samples of the suspension were stored under 2 storage conditions, room temperature (25 °C and 60% relative humidity) and accelerated stability chambers (40 °C and 75% relative humidity). Viscosity, pH, organoleptic properties, and microbial contamination were evaluated according to the approved specifications. High-performance liquid chromatography was used for the analysis and quantification of rosuvastatin in selected samples. Microbiological investigations were also conducted.

Results. The prepared suspension showed acceptable organoleptic properties. It showed complete release of rosuvastatin within 15 minutes. The pH of the suspension was 9.8, which remained unchanged during the stability studies. The microbiological investigations demonstrated that the preparation was free of any microbial contamination. In addition, the suspension showed stability within at least the period of use of a 100-mL rosuvastatin bottle.

Conclusion. Extemporaneously prepared rosuvastatin 20-mg/mL suspension was stable for 30 days when stored at room temperature.

Keywords: extemporaneous, rosuvastatin, stability, suspension

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Throughout the world, atherosclerosis is considered a major underlying cause of cardiovascular disease, including ischemic heart disease, ischemic stroke, and peripheral vascular disease.¹ Atherosclerosis is the thickening of the arterial wall due to the formation of a stiff atherosclerotic plaque that progressively narrows the lumen of the artery and reduces its flexibility, resulting in progressive organ ischemia. In many cases, the plaque can rupture, and a blood clot can quickly form at the lesion site, resulting in acute vessel occlusion.^{2,3} A cornerstone in the pathogenesis of atherosclerosis is the elevation of low-

density-lipoprotein (LDL) cholesterol levels as well as, to a lesser extent, a decline in high-density-lipoprotein cholesterol levels.^{4,5}

Several underlying abnormalities in lipid metabolism can result in high serum LDL cholesterol levels, which are thought to be largely due to an interaction between lifestyle habits and genetics.^{6,7} High LDL cholesterol levels can also be due to autosomal dominant heterozygous-homozygous familial hypercholesterolemia, which is associated with the inheritance of defective LDL receptor genes that restrict the clearance of LDL cholesterol from the blood.⁸ Several other familial dyslipidemias have also

been described, such as familial dysbetalipoproteinemia and familial combined hyperlipidemia.^{9,10} The goal of atherosclerosis treatment is to lower the total and LDL cholesterol levels to prevent atherosclerotic ischemic complications. In addition to lifestyle modifications, pharmacologic intervention is recommended for many patients. Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are the most effective medications for lowering serum cholesterol.¹¹ They inhibit cholesterol synthesis in hepatocytes and induce the expression of LDL cholesterol receptors on the surface of these cells, increasing the uptake of LDL cholesterol from the blood. Statins can also lower triglyceride levels to a certain extent.¹²

Rosuvastatin is the most effective statin for lowering serum LDL cholesterol.^{13,14} Oral administration of rosuvastatin under fasting conditions in adults resulted in peak plasma drug levels within 3–5 hours and an elimination half-life of 16–19 hours.^{15,16} As with the treatment of any illness, patient adherence is a major factor in treatment success, but adherence can be hindered by many factors, such as difficulty in swallowing tablets.¹⁷ In most countries, statins are only available as solid dosage forms. Recently, Rosemont Pharmaceuticals launched 2 approved strengths of simvastatin oral suspensions. Both strengths were found to be stable for 1 year when stored in the original sealed bottle and for 1 month after opening the bottle.¹⁸ However, this new suspension is unavailable in many countries. In addition, some physicians may prefer rosuvastatin over simvastatin due to its higher efficacy and longer plasma half-life.^{13,14,19} Therefore, the development of a stable rosuvastatin liquid formulation for extemporaneous use would be of great benefit for patients who have difficulty swallowing tablets. This study evaluated the stability of an extemporaneously prepared rosuvastatin suspension stored over 30 days under various storage conditions.

KEY POINTS

- Rosuvastatin is the most effective statin for lowering serum low-density-lipoprotein cholesterol levels but the commercially available oral suspension is not available worldwide.
- Extemporaneously prepared rosuvastatin 20-mg/mL suspension was stable for 30 days when stored at room temperature.
- The availability of a stable extemporaneously prepared rosuvastatin solution will allow hospitals and community pharmacies to provide rosuvastatin for pediatric and elderly patients with swallowing difficulties.

Methods

Sample preparation. Suspensions were extemporaneously prepared to a final concentration of 20 mg/mL (0.4% w/v) using rosuvastatin in 40-mg tablets.³ Details of the procedure are provided in the appendix. Samples were taken for initial analysis, and the remaining suspension was stored at room temperature (25 °C and 60% relative humidity) and under accelerated conditions (40 °C and 75% relative humidity) in order to assess the stability of the suspension.

Six bottles of rosuvastatin suspension were prepared; 3 bottles were stored at room temperature and 3 under accelerated conditions. A 5-mL sample was withdrawn from each of the 6 bottles immediately after preparation (time 0) and at each time point of the analysis. The samples were assayed in triplicate using a stability-indicating high-performance liquid chromatographic (HPLC) method.

The suspension was tested for several properties, including organo-

leptic properties, viscosity, dissolution behavior, pH, and microbial contamination.

HPLC method. The amount of rosuvastatin in the prepared suspension was assessed using an HPLC analytic method. The experimental conditions were optimized on an HPLC instrument,^m which included a C₁₈ chemically bonded column.¹ The optimum mobile phase was prepared by mixing 0.02 M potassium dihydrogen phosphate buffer, acetonitrile, and methanol (400:300:300 v/v). The mobile phase was filtered through a 0.45- μ m filter and was degassed by sonication before use. The wavelength was set to 248 nm. The flow rate used was 0.8 mL/min, and the injection volume was 20 μ L. The diluent was prepared by mixing acetonitrile and water in a 1:1 ratio. Peak quantification was obtained by comparing sample and standard peak area ratios as a function of concentration. Weights were measured using a balance,ⁿ and pH was identified using a pH meter.^o

Analytic validation. The method was validated in accordance with the International Conference on Harmonization guidelines.²⁰ Variables such as system suitability, selectivity, linearity, range, accuracy (recovery), and precision (repeatability) were validated. This analytic procedure validation was conducted using 3 trials of the product and 1 trial of the standard solution. The purpose of this study was to establish that the rosuvastatin suspension assay method is effective and reproducible. The dissolution test method for rosuvastatin suspension, based on the assay test method, was also validated.

First, to prepare the rosuvastatin stock solution, 43.2 mg of rosuvastatin^k was transferred to a 100-mL volumetric flask, 80 mL of diluent was added, and the mixture was stirred and sonicated until rosuvastatin dissolved completely. The diluent was added to make 100 mL total, and the solution was mixed well. Next, to prepare the rosuvastatin standard solution, 5 mL of stock solution was transferred to a 50-mL volumetric flask, and the vol-

ume was brought to 50 mL with the addition of mobile phase. The solution was mixed well for homogenization.

Sample preparation. Five milliliters of the compounded suspension was transferred to a 100-mL volumetric flask, after which 75 mL of diluent was added. The mixture was shaken and sonicated for 30 minutes and left to cool to room temperature. The volume was brought to 100 mL with the addition of diluent and then mixed well for homogenization. Next, 5 mL of the supernatant was transferred to a 50-mL volumetric flask, and the mobile phase was added to bring the volume to 50 mL. The solution was filtered through a nylon filter with a pore size of 0.45- μ m or finer porosity. The first 10 mL was rejected; the remaining filtrate was used as the assay preparation.

System suitability. The suitability of the system was determined by injecting 20 μ L of rosuvas-tatin standard solution 6 times to yield a final concentration of rosuvas-tatin 40 μ g/mL. According to the chromatograms, variables such as injection precision for standard solution, tailing factor for standard solution, and theoretical plates for standard solution were calculated. The precision for the standard solution was 0.22 with a limit of <2%, the tailing factor was 1.21 with a limit of <2, and theoretical plates were 4,715 min/cm with a limit of >2,000.

Dissolution study. An in vitro dissolution study was conducted using the reported Food and Drug Administration (FDA) dissolution method for rosuvas-tatin tablets.²¹ To conduct this test, a dissolution apparatus^p was used at a paddle speed of 50 rounds/min. The dissolution medium was 900 mL of 0.05 M sodium citrate^m buffer (pH 6.6 \pm 0.05). The dissolution profile was evaluated under test conditions using deaerated media. This dissolution apparatus^p was maintained at 37 $^{\circ}$ C for the entire study. Five milliliters of the suspension was placed in each paddle. Samples (10 mL) were withdrawn periodically at 10, 20, 30, and 45 minutes after mixing, after which the

same volume of the dissolution medium was replaced. The similarity and nonsimilarity factors (f_2 and f_1 , respectively) were not calculated, since the release of rosuvas-tatin from both the suspension and tablets was higher than 85% after 15 minutes and this is in accordance with FDA guidelines for dissolution testing.²²

Physical stability. Once the suspension was compounded, it was stored in a graduated cylinder; sedimentation was measured at 0, 0.5, 1, 2, and 24 hours. The height of the sediment was measured when there was no change in 3 consecutive readings. The sedimentation volume (F) was calculated using $F = V_u/V_o$, where V_u and V_o are volumes of sediment and suspension, respectively.

The suspension was also tested for the ease of redispersion. Accordingly the suspension was placed in graduated cylinders and rotated periodically 360 degrees until thorough dispersion was achieved. The number of rotations needed for complete redispersion was registered, and the suspension was visually checked for homogeneity and caking at the bottom of the cylinder.

The viscosity of samples was determined with a viscometer^q at different speeds (5, 10, 20, 50, and 100 rpm) after a 1-minute rotation at room temperature. The flow type of the suspension was characterized using the following equation²³:

$$F^N = \eta G$$

where F is the shear stress, G is the shear rate, N is an exponential constant, and η is a viscosity coefficient.

Microbial contamination testing. The culture medium was prepared by dissolving 28 g of nutrient agar dehydrated powder in 1 L of distilled water. The prepared suspension was warmed to boiling under vigorous mixing. After that, the solution was autoclaved at 125 $^{\circ}$ C for 15 minutes. Next, the solution was poured in sterile petri dishes and refrigerated for 24 hours. After refrigeration, a 0.1-

mL sample was removed from each compounded rosuvas-tatin suspension with a pipette and placed on petri dishes, which were incubated at 37 $^{\circ}$ C for 48 hours to check for the presence of *Escherichia coli*, aerobic bacteria, and yeast and molds.²⁴

Results

A formulation of rosuvas-tatin suspension was prepared using crushed tablets as a source of the active pharmaceutical ingredient. The formulation was tested for several properties, including pH, organoleptic properties, microbial contamination, and dissolution behavior. The suspension showed suitable pourability and registered a non-Newtonian viscosity. In fact, the N value of the suspension was found to be higher than 1, resulting in pseudoplastic flow. The sedimentation volume was close to 0.87 after 24 hours of suspension formation. The redispersibility test showed easy redispersion after only 4 revolutions without any sign of caking.

Regarding the analytic method used, all validation measurements were within acceptable limits. Specificity was tested, and no interference between the peak of rosuvas-tatin and any other peaks was seen. Acceptable linearity was demonstrated by a correlation coefficient of $r^2 = 0.99996$ and a y-intercept of 3369.95. The accuracy of all measurements ranged from 98.8% to 102.0%. Finally, precision was proven with a coefficient of variation of 0.71 (maximum limit of 2.0%). System suitability was assessed, and factors such as precision, tailing factor, and theoretical plates were within the acceptable limits. The related-substance test was conducted according to the European Pharmacopoeia method of analysis, and all of the results were within the acceptable limits (Table 1).²⁵

The results of dissolution testing of the rosuvas-tatin suspension were comparable to those with the original tablet used in its compounding. In fact, both formulations (suspension and tablets) released more than 85%

of the drug within 15 minutes. Accordingly, there was no need to test for similarity and nonsimilarity factors. Once the dissolution was assessed and found to be comparable with the corresponding solid formulation, rosuvastatin suspension was stored at room temperature and accelerated conditions in order to assess its stability. The suspension was chemically stable when stored at room temperature for 30 days. There was no appreciable change in pH, which remained around 10 ± 0.15 , and the mean percentage of the initial rosuvastatin concentration remaining was $99\% \pm 0.2\%$. When stored in accelerated conditions, the rosuvastatin suspension showed complete degradation within the first week of storage.

The rosuvastatin suspension was found to be free of any microbial contamination at 30 days (Table 2).

Discussion

An extemporaneously prepared suspension of rosuvastatin was found to be stable when stored at room temperature for 30 days. Stability was de-

termined as keeping more than 95% of the initial rosuvastatin concentration. At least 97.9% of the initial concentration of the rosuvastatin suspension remained throughout the 30-day study period. There was no detectable change in color, odor, or taste, and no visible microbial growth was observed in any sample. The preparation was a well-distributed suspension after gentle shaking and was palatable with a slight aftertaste. All related substances and enantiomers remained within acceptable limits over the 30-day period. No appreciable change in mean pH occurred in any of the tested samples, regardless of storage temperature.

The bioavailability of the rosuvastatin suspension in this study was not evaluated; however, the absorption and therapeutic efficacy of a drug in a suspension compounded from crushed tablets are unlikely to differ from those of the original dosage form used in its compounding.

Conclusion

Extemporaneously prepared rosuvastatin 20-mg/mL suspension was

stable for 30 days when stored at room temperature.

Acknowledgments

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Disclosures

The authors have declared no potential conflicts of interest.

^aCrestor film-coated tablets (40 mg/tablet), AstraZeneca, Cheshire, United Kingdom, lot KD065.

^bOrange flavor, Givaudan, Dübendorf, Switzerland.

^cCherry, Firmenich, Geneva, Switzerland, lot 40064.

^dAspartame, Ajinomoto, Tokyo, Japan, lot E502020.

^eSodium saccharin, Tianjin Food Co., Tianjin, China, lot 20140723.

^fTrisodium citrate, Weifang Ensigan Industry, Changle, China, lot ST1503066.

^gSodium hydroxide, Merck, Darmstadt, Germany.

^hGuar gum, CP Kelco, Atlanta, GA, lot RG250/15/1590.

ⁱSorbitol instant, Sugat Ltd., Kiryat Gat, Israel, lot 6145.

^jMilky high density polyethylene bottles, Plastic-LOG, Ashdot, Israel.

^kEuropean Pharmacopoeia (EP) rosuvastatin calcium, Lee Pharma, Hyderabad, India, lot RCFP14019.

^lLaChrom, model L-7100 pump, L-7200 autosampler, L-7300 column oven, DAD L-7450 photo diode array detector, and D-7000 software HSM (version 3.1), Merck Hitachi, Tokyo.

^mOctadecyl silane column (150 mm \times 4.6 mm i.d., 5- μ m particle), ACE, Aberdeen, United Kingdom.

ⁿOhaus balance, United Technology Trade Corp., Staten Island, NY.

^oToledo GmbH, Greifensee, Switzerland.

^pModel DT 70, Erweka, Heusenstamm, Germany.

^qRotational viscometer, Brookfield, Middleboro, MA.

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Table 1. Summary Results of Related Substances Found in Rosuvastatin Suspension

Impurity	Results, %	Acceptable Limit, %
Impurity A	0.158	≤ 0.2
Impurity B	0.208	≤ 0.5
Impurity C	0.189	≤ 0.8
Unspecified impurities	0.072	≤ 0.1 for each
Total impurities	0.630	≤ 1.2
Enantiomeric purity (impurity G)	0.078	≤ 0.1

Table 2. Results of Microbial Testing After 30 Days of Storage at Room Temperature^a

Microbe	Results	Limits
<i>Escherichia coli</i> bacteria	Negative	None
Mold and yeasts	≤ 10 CFU/mL	≤ 10 CFU/mL
Total aerobic bacteria count	$\leq 10^2$ CFU/mL	≤ 100 CFU/mL

^aCFU = colony-forming units.

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Appendix—Procedure for compounding rosuvastatin 20-mg/mL suspension

To prepare 100 mL of the desired rosuvastatin suspension (0.4% w/v), the following procedure was used:

- Crush 10 rosuvastatin 40 mg tablets^a using a mortar and pestle.
- Under continual mixing and trituration, combine 0.133 g of orange flavor,^b 0.0055 g of cherry flavor,^c 0.19 g of aspartame,^d 0.19 g of sodium saccharin,^e 0.33 g of trisodium citrate,^f 0.4 g of sodium hydroxide,^g and 0.5 g of guar gum.^h
- Keep mixing and gradually add 23.73 g of sorbitol instant.ⁱ
- Once the dry powder is well mixed, add reverse osmosis water^j and mix well until a pourable mass is achieved.
- Add reverse osmosis water^j again to bring the suspension to the desired volume.
- Pour into plastic milky high density polyethylene bottles^k and close tightly.